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*****CPCH0162364P

Patent Office of the People's Republic of China

Address : Receiving Section of the Chinese Patent Office, No. 6 Tucheng Road West, Haidian District, Beijing. Postal code: 100088

Applicant	AJINOMOTO CO., INC.			Seal of Examiner	Date of Issue: January 16, 2004
Agent	China Patent Agent (H.K.) Ltd.				
Patent Application No.	00806019.3	Application Date	April 7, 2000	Exam. Dept.	
Title of Invention	L-AMINO ACID-PRODUCING BACTERIUM AND METHOD FOR PRODUCING L-AMINO ACID				

First Office Action

(PCT application entering into the national phase)

1. ☑ Under the provision of Art. 35, para. 1 of the Patent Law, the examiner has made an examination as to substance of the captioned patent application for invention upon the request for substantive examination filed by the applicant on_____.

☐ Under the provision of Art. 35, para. 2 of the Patent Law, the Chinese Patent Office has decided to conduct an examination of the captioned patent application for invention on its own initiative.

2. ☑ The applicant requests that
the filing date Apr. 9, 1999 at the JP Patent Office be taken as the priority date of the present application,
the filing date Jun. 16, 1999 at the JP Patent Office be taken as the priority date of the present application,
the filing date Dec. 24, 1999 at the JP Patent Office be taken as the priority date of the present application.

3. ☐ The following amended documents submitted by the applicant cannot be accepted for failure to conform with Art. 33 of the Patent Law:
☐ the Chinese version of the annex to the international preliminary examination report.
☐ the Chinese version of the amended documents submitted according to the provision of Rule 19 of the Patent Cooperation Treaty.
☐ the amended documents submitted according to the provision of Rule 28 or Rule 41 of the Patent Cooperation Treaty.

☐ the amended documents submitted according to the provision of Rule 51 of the Implementing Regulations of the Patent Law.

See the text portion of this Office Action for detailed reasons why the amendment cannot be accepted.

4. ☑ Examination is conducted on the Chinese version of the initially-submitted international application.

☐ Examination is conducted on the following document(s):

☐ page _____ of the description, based on the Chinese version of the initially-submitted international application documents;

page _____ of the description, based on the Chinese version of the annex to the international preliminary examination report;

page _____ of the description, based on the amended documents submitted according to the provision of Rule 28 or Rule 41 of the Patent Cooperation Treaty;

page _____ of the description, based on the amended documents submitted according to the provision of Rule 51 of the Implementing Regulations of the Patent Law.

☐ claim(s) _____ , based on the Chinese version of the initially-submitted international application documents;

claim(s) _____ , based on the Chinese version of the amended documents submitted according to the provision of Rule 19 of the Patent Cooperation Treaty;

claim(s) _____ , based on the Chinese version of the annex to the international preliminary examination report;

claim(s) _____ , based on the amended documents submitted according to the provision of Rule 28 or Rule 41 of the Patent Cooperation Treaty;

claim(s) _____ , based on the amended documents submitted according to the provision of Rule 51 of the Implementing Regulations of the Patent Law.

☐ Fig(s) _____ , based on the Chinese version of the initially-submitted international application documents;

Fig(s) _____ , based on the Chinese version of the annex to the international preliminary examination report;

Fig(s) _____ , based on the amended documents submitted according to the provision of Rule 28 or Rule 41 of the Patent Cooperation Treaty;

Fig(s) _____ , based on the amended documents submitted according to the provision of Rule 51 of the Implementing Regulations of the Patent Law.

5. ☑ The following reference document(s) is/are cited in this Office Action (its/their serial

number(s) will continue to be used in the subsequent course of examination):

Serial No	Number or Title(s) of Document(s)	Date of Publication (or filing date of interfering application)
1	EP 0035831A2	Date Sept. 16, 1981
2	EP 0435132A1	Date Jul. 3, 1991
3	APPLIED AND ENVIRONMENTAL MICROBIOLOGY, VOL. 58, NO. 9, Pages 2806-2814	Date Sept. 1992
4	MICROBIOLOGY, VOL. 143, PART 3, PAGES 899-907	Mar. 1997
5	NUCLEIC ACIDS RESEARCH, VOL. 18, NO. 21, PAGE 6421	Nov. 1990
6	THE JOURNAL OF BIOLOGICAL CHEMISTRY, VOL. 259, NO. 23, PAGES 14829-14834	Dec. 1984

6. Concluding comments on the examination:

☐ On the description:

☐ What is stated in the application comes within the scope of that no patent right shall be granted as prescribed in Art. 5 of the Patent Law.

☐ The description is not in conformity with the provision of Art. 26, para. 3 of the Patent Law.

☑ On the claims:

☐ Claim(s) _____ come(s) within the scope of that no patent right shall be granted as prescribed in Art. 25 of the Patent Law.

☑ Claim(s) 1, 17, 19, 21, 23 has/have no novelty as prescribed in Art. 22, para. 2 of the Patent Law.

☑ Claim(s) 2-15 has/have no inventiveness as prescribed in Art. 22, para. 3 of the Patent Law.

☐ Claim(s) _____ has/have no practical applicability as prescribed in Art. 22, para. 4 of the Patent Law.

☑ Claim(s) 16-25 is/are not in conformity with the provision of Art. 26, para. 4 of the Patent Law.

☑ Claim(s) 16-25 is/are not in conformity with the provision of Art. 31, para. 1 of the Patent Law.

☐ Claim(s) _____ is/are not in conformity with the provisions of Rules 20 to 23 of the Implementing Regulations.

☐ Claim(s) _____ is/are not in conformity with the provision of Art. 9 of the Patent Law.

☐ Claim(s) _____ is/are not in conformity with the provision of Rule 12, para. 1 of the Implementing Regulations.

See the text portion of this Office Action for detailed analysis of the above concluding comments.

7. Based on the above concluding comments, the examiner deems that

☐ the applicant should make amendment to the application document(s) according to the requirements put forward in the text portion of this Office Action.

☑ the applicant should expound in his/its observations why the captioned patent application is patentable and make amendment to what is not in conformity with the provisions pointed out in the text portion of this Office Action, otherwise, no patent right shall be granted.

☐ the patent application contains no substantive content(s) for which a patent right may be granted. If the applicant has no sufficient reason(s) to state or his/its stated reason(s) is/are not sufficient, said application will be rejected.

☐

8. The applicant should note the following items:

(1) Under Art. 37 of the Patent Law, the applicant should submit his/its observations within **four** months from the date of receipt of this Office Action; if, without any justified reason(s), the time limit for making written response is not met, said application shall be deemed to have been withdrawn.

(2) The amendment made by the applicant to said application should be in conformity with the provision of Art. 33 of the Patent Law, the amended text should be in duplicate and its form should conform with the related provisions of the Guide to Examination.

(3) If no arrangement is made in advance, the applicant and/or the agent shall not come to the Chinese Patent Office to have an interview with the examiner.

(4) The observations and/or amended text should be sent to the Receiving Section of the Chinese Patent Office by mail or by personal delivery. If not sent to the Receiving Section by mail or by personal delivery, the document(s) will have no legal effect.

9. This Office Action consists of the text portion totalling 8 page(s) and of the

following attachment(s):

☑ 6 copy(copies) of the reference document(s) totalling 57 page(s).

Examination Dept. No. ____ Examiner ____

9016

Our Ref: CPCH0162364P
Appl No: 00806019.3

Text of the First Office Action

According to the description, the present application relates to an L-amino acid-producing bacterium and a method for producing an L-amino acid.

After examination, comments are made as follows.

1. Claim 1 does not comply with the provision on novelty as stipulated under Article 22-Paragraph 2 of the Patent Law.

Reference document 1 (EP0035831) discloses three kinds of genetically modified recombinant *Methylophilus methylotrophus*, which are all obtained by transferring gdh (glutamate dehydrogenase gene) derived from *E.Coli*, after connecting it with a vehicle, into a *mycelidium Methylophilus methylotrophus* NCIB10515. Since there is no GDH enzyme in *Methylophilus methylotrophus*, the recombinant bacterium obtained through the above pathway has the ability of directly synthesizing L-glutamic acid by using α-oxoglutarate (see page 1 to page 7, line 26, and examples 1 and 2). That is, reference document 1 has disclosed the *Methylophilus* bacterium having the L-amino acid-producing ability. Therefore, claim 1 does not possess novelty.

2. Claim 2 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

Reference document 1 discloses a recombinant *Methylophilus methylotrophus* having the ability of directly synthesizing L-glutamic acid by using α-oxoglutarate. As is known to persons skilled in the art, by using oxaloacetic acid and glutamic acid, lysine, isoleucine and threonine can be obtained via certain metabolism pathway; and by using pyruvic acid, valine and leucine can be obtained. When the enzyme needed for the above said metabolism pathway is not deleted from the primitive *Methylophilus methylotrophus*, the above said amino acids can surely be produced from the recombinant *Methylophilus methylotrophus* as disclosed in

reference document 1. Therefore, on the basis of the combination of reference document 1 and the said common knowledge, persons skilled in the art will find it obvious to obtain the technical solution claimed in said claim. As a result, the technical solution claimed in claim 2 neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

3. Claim 3 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

As is known to persons skilled in the art, in order to obtain a maximum amount of a product, such as amino acids, they need to apply a variety of means to adjusting the metabolism pathways that are related to the synthesis thereof. For example, they need to culture strains deficient in metabolism. During the pathway of synthesizing lysine from glutamic acid *Corynebacterium*, persons skilled in the art synthesize a large amount of lysine by deleting homoserine dehydrogenase to remove the synergetic feedback inhibition by threonine and lysine against AK (aspartokinase). For another example, they need to synthesize a large amount of the target product by using structure analogs of amino acids. In the process of synthesizing threonine from Uranidin *Brevibacterium*, such structure analog of threonine AHV is used to remove the feedback inhibition against AK1 and HSDH1 (homoserine dehydrogenase 1) and to accumulate threonine. Therefore, when claim 1 is not inventive, persons skilled in the art will find it obvious to obtain the technical solution of claim 3 on the basis of the above common knowledge. As a result, the technical solution claimed in claim 3 neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

4. Claim 4 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

As is known to persons skilled in the art, the producing bacterium screened out via the above pathways, which can produce a large amount of target products, usually has an enhanced enzymatic activity because of a mutation of the structural genes of the key enzymes in the metabolism pathway. Therefore, when claim 1 is not inventive, persons skilled in the art will find it obvious to obtain

the technical solution of claim 4 on the basis of the above common knowledge. As a result, the technical solution claimed in claim 4 neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

5. Claim 5 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

As is known to persons skilled in the art, in the metabolism pathway for synthesizing lysine from bacterium, aspartokinase AK and dihydrodipicolinate synthase are key enzymes. The structural gene of aspartokinase has an enhanced activity because of the mutation taking place in screening out a mutant deficient in threonine in order to synthesize lysine. At the same time, by enhancing the activity of dihydrodipicolinate synthase activity, the ability of the strains for synthesizing lysine will be greatly improved. Therefore, when claim 1 is not inventive, persons skilled in the art will find it obvious to obtain the technical solution of claim 5 on the basis of the above common knowledge. As a result, the technical solution claimed in claim 5 neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

6. Claims 6 and 7 do not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

Referring to the comments on claim 5 for detailed comments.

7. Claim 8 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

The three enzymes recited in claim 8 are all enzymes used in the synthesis of lysine. Though they are not key enzymes in the metabolism process, the enhancement of the activity of the above enzymes alone or simultaneously will greatly increase the amount of the lysine synthesized. Therefore, when claims 5-7 are not inventive, persons skilled in the art will find it obvious to obtain the technical solution of claim 8 on the basis of the above common knowledge. As a result, the technical solution claimed in claim 8

neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

8. Claim 9 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

As stated above, aspartokinase AK and dihydrodipicolinate synthase DDPS are key enzymes in the lysine synthesizing pathway, and they are easily suffered from the feedback inhibition of the final product lysine in the metabolism pathway. Reference document 1 discloses a genetically recombinant method for introducing gdh into *Methylophilus methylotrophus*, so as to make it have an ability of producing L-amino acid, especially an ability of producing glutamic acid using GDH enzyme. Reference document 2 (EP0435132) discloses that: after connecting the AK enzyme gene lysC and DDPS gene dapA that are free of the feedback inhibition by lysine and introducing them into *Corynebacterium*, the activity of AK and DDPS of the conversion increases by 15 times, and thereby a large amount of lysine can be produced (see the whole of reference document 2). As technically motivated by the above two reference documents, persons skilled in the art will easily think of introducing AK enzyme gene lysC and DDPS gene dapA that are free of the feedback inhibition by lysine into *Methylophilus* bacterium to produce L-lysine. And they can thereby obtain the technical solution of claim 9. Therefore, said claim neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

9. Claim 10 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

As is known to persons skilled in the art, the enzyme stated in claim 10 is a key catalytic enzyme in the process for synthesizing threonine. As claim 1 is not inventive, if persons skilled in the art hope to produce lysine from *Methylophilus* bacterium, they will surely think of enhancing the activity of said enzyme, and thus they may surely produce a large amount of threonine. That is, they will arrive at the technical solution of claim 10. Therefore, said claim neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

11. Claim 11 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

Reference document 1 discloses that all the *Methylophilus* bacteria are *Methylophilus methylotrophus*. Such being the case, when claims 1-10 are not inventive, claim 11 neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

12. Claims 12, 14 and 15 do not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

It is common knowledge to persons skilled in the art to obtain the target product by culturing the producing bacterium for producing the target product in an appropriate medium. Such being the case, when the target strains stated in claims 1-11 are not inventive, claims 12, 14 and 15 neither have prominent substantive features nor represent a notable progress, and thus do not possess inventiveness.

13. Claim 13 does not comply with the provision on inventiveness as stipulated under Article 22-Paragraph 3 of the Patent Law.

Reference document 1 discloses that methanol is used as the carbon source in culturing recombinant *Methylophilus methylotrophus* (see example 2). Such being the case, when claim 12 is not inventive, claim 13 neither has prominent substantive features nor represents a notable progress, and thus does not possess inventiveness.

14. Claims 16-25 relates to the amino acids or nucleotide sequences of five enzymes. Although these five enzymes are enzymes in the metabolism pathway for biosynthesizing lysine, it is by the step catalysis of the five enzymes that lysine is finally synthesized from oxaloacetic acid and glutamic acid. However, since the bases catalyzed by the five enzymes and the products resulted therefrom are different, or in other words, since these enzymes catalyze different reactions respectively, their functions in the whole metabolism pathway are different. In addition, the

structural features of the amino acids and nucleotide sequences corresponding to these five enzymes are different. According to Article 31 of the Patent Law, "two or more inventions belonging to a single general inventive concept can be filed as one application. At the same time, Rule 35 of the Implementing Regulations of the Patent Law further illustrates the meaning of a single general inventive concept, stipulating that such inventions "shall be technically interrelated and contain one or more of the same or corresponding special technical features". The five enzymes of the present application, however, are different both in terms of structural features and of functions, nor do they contain the same or corresponding special technical features. Therefore, the claims corresponding respectively to these five enzymes do not belong to a single general inventive concept. As a result, these claims do not possess unity, and do not comply with the provision of Article 31-Paragraph 1 of the Patent Law.

15. Claim 17 does not comply with the provision on novelty as stipulated under Article 22-Paragraph 2 of the Patent Law.

Reference document 3 (APPLIED AND ENVIRONMENTAL MICROBIOLOGY, vol.58, no.9, September 1992, pages 2806-2814) discloses a nucleotide sequence of the aspartokinase II derived from *Thermophilic Methylotrophic Bacillus* sp., which is hybridizable with the nucleotide sequence stated in claim 17 (b) under a stringent condition. That is, reference document 3 has disclosed all the technical features of claim 17(b). Therefore, said claim does not possess novelty.

16. Claim 19 does not comply with the provision on novelty as stipulated under Article 22-Paragraph 2 of the Patent Law.

Reference document 4 (MICROBIOLOGY, vol.143, PART 3, March 1997, pages 899-907) discloses a nucleotide sequence of aspartic acid semialdehyde dehydrogenase derived from *Peudomonas aeruginosa*, which is hybridizable with the nucleotide sequence stated in claim 19 (b) under a stringent condition. That is, reference document 4 has disclosed all the technical features of claim 19(b). Therefore, said claim does not possess novelty.

17. Claim 21 does not comply with the provision on novelty as stipulated under Article 22-Paragraph 2 of the Patent Law.

Reference document 5 (NUCLEIC ACIDS RESEARCH, vol.18, no.21, 11 November 1990, page 6421) discloses a nucleotide sequence of dihydrodipicolinate synthase derived from *Corynebacterium glutamicum*, which is hybridizable with the nucleotide sequence stated in claim 21 (b) under a stringent condition. That is, reference document 5 has disclosed all the technical features of claim 21(b). Therefore, said claim does not possess novelty.

18. Claim 23 does not comply with the provision on novelty as stipulated under Article 22-Paragraph 2 of the Patent Law.

Reference document 6 (THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol.259, no.23, 10 December 1984, pages 14829-14834) discloses a nucleotide sequence of dihydrodipicolinate reductase derived from *Escherichia Coli*, which is hybridizable with the nucleotide sequence stated in claim 23 (b) under a stringent condition. That is, reference document 6 has disclosed all the technical features of claim 23(b). Therefore, said claim does not possess novelty.

19. Claims 16-25 do not comply with Article 26-Paragraph 4 of the Patent Law.

Because of the open-ended expression "comprising" used in technical solutions (a) of claims 17, 19, 21, 23 and 25, the nucleotide sequences claimed in said claims are interpreted as comprising more than the sequences shown in SEQ ID NO 5, 7, 9, 11 and 13, i.e., comprising other sequences. Since the description only discloses SEQ ID NO 5, 7, 9, 11 and 13, such protection scopes cover too many compounds. According to the disclosure of the description, however, persons skilled in the art cannot foresee that the applicant has obtained all the stated compounds, or in other words, all the amino sequences can fulfill the purpose of the invention. Therefore, claims 6 and 7 are not supported by the description, and thus do not comply with Article 26-Paragraph 4 of the Patent Law. The applicant should **delete "comprising" from**

technical solutions (a) of claims 17, 19, 21, 23 and 25.

In addition, the **technical solutions (B)** of claims 16, 18, 20, 22 and 24 do not comply with Article 26-Paragraph 4 of the Patent Law either, due to the presence of "comprising" therein.

After amending the claims in accordance with the above comments, the applicant should **amend the technical solution part of the description correspondingly**, so that the disclosure in this part can reflect the technical solution claimed in the independent claims of the present application. Only by doing that will the present application comply with Rule 18-Paragraph 1 (3) of the Implementing Regulations of the Patent Law (see the Guidelines for Examination, Part II, Chapter 2, Section 2.2.4).

For the above reasons, the present application cannot be granted a patent right according to its current documents. The applicant should amend the application documents in accordance with the comment above and remove all the defects indicated in this office action. Amendments shall conform to the provision of Article 33 of the Patent Law and may not go beyond the scope of the initial description and claims. Otherwise, this application will be rejected. **The applicant is required to provide a photocopy of the original text** to which amendments have been made, **with all the amendments marked out in color.**

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